Anaphylaxis in Y2K

Travis B. Richardson, M.D.
Internal Medicine Resident
Walter Reed Army Medical Center

09/13/16

Goals of Presentation

- Definition
- Epidemiology
- Pathophysiology
- Clinical Manifestation
- Differential Diagnosis
- Diagnosis/Etiology
- Management
- Prevention

Definition

"An exaggerated, life-threatening,often times abrupt, hypersensitivity reaction to a previously encountered antigen"

- Anaphylactoid vs. anaphylaxis
- Coined originally about 100 yrs ago - Portier and Richet
- Specifically for IgE-mediated reactions with release of mast cell products

Origin of “Anaphylaxis”

- 1901, Portier and Richet studied immunization of animals against sea anemones toxins. At the time, the Prince of Monaco was an avid supporter of scientific research, and the initial studies were done in the Mediterranean Sea on his yacht. Drs. Portier and Richet initiated their studies looking at the stings from Portuguese Man-O-Wars, but finished using sea anemones which were readily available in Paris.

Origin Continued

- Upon examining the immune response to the toxins they discovered something unexpected: “. . . the dogs which had recovered were intensely sensitive, and died a few minutes later after small doses. . . These two factors, a) increased sensitivity to a poison after previous injection of the poison, and b) an incubation period necessary for this state of increased sensitivity to develop constitute the two essential and sufficient conditions for anaphylaxis.”

Epidemiology

- No specific role for age, race, sex, or occupation has been demonstrated in susceptibility except insofar as particular exposure patterns may be due to these variables (e.g. latex exposure to medical personnel)
- General and specific rates difficult to state with certainty

Epidemiology (cont)

- Data on epidemiology are available for only selected groups and not general population
- Studies complicated by: varying definitions, patient surveys yielding false (-) and false (+), few studies, underreported, and extent in general population can not be determined easily

Epidemiological studies

- Sorenson, et al. 1989, retrospective - 48,000 cases over 13 years, 20 cases found, 3.2 cases per 100,000 person years
- Klein, et al 1995, retrospective, ED visits over 4 months - 90 cases per 100,000
- Yocum, et al 1999, retrospective-population based study over 5 years - 154 cases from 1255 Olmstead Co. residents

Yocum, et al.

- 21 per 100,000 person years
- 7% hospitalization rate
- 53% had history of atopy
- 1 patient died (0.65% case fatality rate)
- Suspected allergen 68% of time
- First study to examine overall incidence of anaphylaxis in a defined community

Pathophysiology

Direct result of systemic release of mediators by activated mast cells

- IgE mediated**
- Immune complex mediated
- Abnormalities of arachidonic metabolism
- Direct degranulation of mast cells
- Idiopathic

Pathophysiology

- Mast cells with IgE receptors on surface
- Individual exposed to antigen, develops specific IgE to antigen
- Upon re-exposure, if specific IgE in high enough concentration, antigen will cross-link IgE on surface, activating mast cell and releasing chemical mediators
- Mediators: HISTAMINE, leukotrienes (C,D,E), PAF, ECF-A, IL's, TNF, chymase, tryptase

Pathophysiology (cont.)

- Chemical mediators vaso-active, leading to smooth muscle spasm, bronchospasm, mucosal edema and inflammation, and increased capillary permeability, which leads to symptomotology seen in anaphylaxis
- HISTAMINE known responsible agent for most of manifestations

Clinical Manifestations

Manifested by number of non-specific findings as well as specific organ changes

- NONSPECIFIC CHANGES
- Metallic or “funny” taste in mouth
- Sense of warmth, flushing particularly in intertriginal areas
- Some patients describe feeling of impending doom

Clinical Manifestations (cont)

- ORGAN-SPECIFIC CHANGES
- Cutaneous
- Respiratory
- Cardiovascular
- Gastointestinal
- Miscellaneous

Clinical manifestations (cont)

- **Cutaneous -** erythema, flushing (face and upper chest), urticaria, angioedema
- **Respiratory** - upper airway obstruction (laryngeal edema), lower airway involvement ->-> stridor, hoarseness, wheezing, dysphagia, inability to handle oral secretions (2/3 of deaths in one series)
- **Cardiovascular -** tachycardia, arrythmias, hypotension, syncope, ischemia, infarction

Clinical manifestations (cont)

- **Gastrointestinal** - cramping, nausea, vomiting, diarrhea (may be bloody)
- **Miscellaneous** - rhinorrhea, nasal and palatal pruritis, conjuntival injection, weakness, dizziness, diaphoresis
- Biphasic response**
- **DEATH!**

Differential Diagnosis

- Vasovagal reactions/syncope
- Hereditary Angioedema
- Serum Sickness
- Carcinoid Syndrome
- Mastocytosis
- Globus Hystericus (lump in the throat)

Diagnosis

- The diagnosis is usually apparent, because its rapid onset and severe manifestations are rarely overlooked or missed
- Accurate history and physical (usually in setting of appropriate signs/symptoms within minutes after exposure to agent
- When only portion of full spectrum present difficult to exclude toxicologic, non-immunologic, or idiosyncratic reaction

Diagnosis (cont)

- Usually history is so specific that no diagnostic tests are warranted
- Tests include allergy skin tests, in vitro specific IgE tests, and/or challenge tests
- Skin testing more sensitive than in vitro tests
- Skin testing diagnostic test of choice for most potential causes (drugs, foods, insects)
- Further tests may be necessary if Dx is ??

Diagnosis (cont)

- May consider checking for mediators in blood indicative of a mast-cell mediated event (histamine and tryptase)
- Histamine - plasma level maximal at 15 minutes; return to baseline by 30 to 60 minutes
- Beta-Tryptase - normal levels undetectable; peak at 1-2 hrs; may be detected 6-12 hrs after an episode

Etiology

- Theoretically any substance that we may come into contact with may cause anaphylaxis
- Large list of agents or materials associated with anaphylaxis or anaphylactoid reaction

Etiology (cont)

- Beta-lactam antibiotics
- Hymenoptera venom
- Foods (nuts, eggs, fish)
- Allergen immunotherapy
- Latex
- Exercise-induced
- Insulin
- Protamine
- ASA/NSAIDS
- Local anesthetics
- General anesthesia
- IV fluorescein
- Radiocontrast material
- Opiod analgesics
- Ethylene oxide (dialysis)
- Avian based vaccines
- IDIOPATHIC

Etiology (cont)

- **Beta-lactam antibiotics**
- Most frequent cause of anaphylaxis in US
- Cause of about 75% of deaths
- IV route more likely to cause reaction
- Carbepenems should be considered cross-reactive; monobactams rarely cross-react
- Cephalosporins risk is about 10% or less; first generation may pose greater risk

Etiology (cont)

- **Hymenoptera venom**
- Deaths rank second only to penicillin
- Two major subgroups (vespids and apids)
- Remove stinging apparatus if possible; should be flicked off, not squeezed
- Skin testing available; serum tests not as sensitive and more expensive
- Venom immunotherapy highly effective; continue for 3-5 years

Etiology (cont)

- **Exercise-Induced Anaphylaxis**
- Must differentiate exercise-induced asthma and cholinergic urticaria
- Often requires cofactor of particular food (celery, carrots, wheat) before exercise
- Usually history of atopy (personal or family)
- Prophylactic medications of limited value

Etiology (cont)

- **Latex**
- Health care workers, patients, manufacturers
- Cross reactivities with foods (avacados, bananas, chestnuts)
- Therapy is latex free environment
- Nearly impossible to maintain latex free environment

Etiology (cont)

- **Post-immunotherapy**
- One of most frequent causes seen in any Allergy/Immunology clinic
- Rates about 3-6 per 1000 injections
- Case fatality rate in UK and US sometimes more than 1 per year
- Generally, cases are mild and quickly respond to epinephrine

Management

- EPINEPRINE!!
- Beta agonists
- Oxygen
- Antihistamines (H1 and H2)**
- Corticosteroids**
- Supportive therapy:

  IV fluids, vasopressors, aminophylline, glucagon

Management (cont)

- **Epinephrine**
- Dose 0.2 ml to 0.5 ml of 1:1000 dilution SC or IM
- Repeat every 15 min as tolerated and as needed
- Evidence supports more rapid and higher plasma concentration after IM dosing
- IV may be used in refractory cases (1:10,0000 dilution)

Management (cont)

- **Corticosteroids**
- Role in acute treatment unclear
- Some advocate early use since action is delayed, so any benefit is achieved earlier
- Those who believe delayed or biphasic anaphylaxis is a major problem advocate early use
- Hydrocortisone 200 to 250 mg IV or Methylprednisolone 50 to 125 mg IV (q6)

Management (cont)

- **Antihistamines**
- Effective for reducing cutaneous manifestations (urticaria)
- Diphenhydramine 25 mg to 50 mg IV q6 hrs (hydroxyzine may also be used)
- No role for acute treatment of pulmonary manifestations
- Use of H2 blockers not as clear until late 80’s to early 90’s

Management (cont)

- **H2 Blockers**
- Effect of histamine on coronaries blocked by H1 antagonists; in contrast H2 receptors mediate effect in atria and ventricles
- Clinical trials done to examine effect of H1/H2 combo in preventing anaphylaxis to morphine, RCM, plasma expanders, and anesthesia agents
- Most data on pretreatment/prophylaxis

Management (cont)

- **H2 Blockers**
- Runge et al, Annals of EM, 1990 (controlled, randomized, double blinded) - Looked at treatment of mild acute allergic reactions; cimetidine +benadryl vs benadryl alone - Showed no difference for pruritis but combo more effective for urticaria

Management (cont)

- **H2 Blockers**
- In the treatment of anaphylaxis; physiologic rationale and series of small clinical trials and case reports suggest that combo blockade should more effective than H1 alone
- All studies looked at cimetidine alone
- No good, large, prospective studies

Management (cont)

- **Glucagon**
- Role in refractory hypotension and/or patients on beta blockers
- Has positive inotropic and chronotropic cardiac effects that are mediated independently of alpha and beta receptors
- cAMP synthesis within myocardium leading to ioncreased rate and force of contraction

Management (cont)

- **Glucagon**
- No well controlled clinical studies justifying routine use exists; only anecdotal case studies
- Overall data supports use in correct setting
- Dose at 1 mg (IV, SC, or IM)
- May run continously 5 ul/min to 15 ul/min

(1 mg in 1L D5W at 5-15 ml/min)

Prevention

- **EPINEPHRINE PEN!!**
  Some kits also with antihistamines
- **MEDICAL ALERT BRACELET**
- **DETERMINE ETIOLOGY**
- **EDUCATION**
  Avoidance of triggers
  Use of epinephrine pen
  Hidden allergens

Prevention (cont)

- **Desensitization**
  -PCN, beta-lactam antibiotics, NSAIDS
- **Immunotherapy**
  -Hymenopterans
- **Prophylaxis**
  -Radiocontrast material
  -Idiopathic Anaphylaxis

SUMMARY

- Anaphylaxis deadly entity but death rare if treated appropriately
- Anaphylaxis vs anaphylactoid
- Most common etiology of anaphylaxis death is PCN followed by insect stings
- Foundation of treatment is EPINEPHRINE
- Any agent/material may potentially cause anaphylaxis

QUESTIONS???